Influence of Population Variation of Physiological Parameters in Computational Models of Space Physiology

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Model Credibility

Verification	Validation	Data Pedigree	Results Uncertainty
Results Robustness	Input Pedigree	Use History	M&S Management

NASA Standard 7009a – Credibility of Models and Simulation

Results Robustness

Sensitivity Analysis: Assesses whether or not the result from an M&S changes in a meaningful way upon relatively slight variations in input parameters.

A Modeling and Simulation (M&S) result is:

- Robust if output is relatively stable with respect to changes in input parameters
- Sensitive if small perturbations of particular input parameters produce dramatic changes in results

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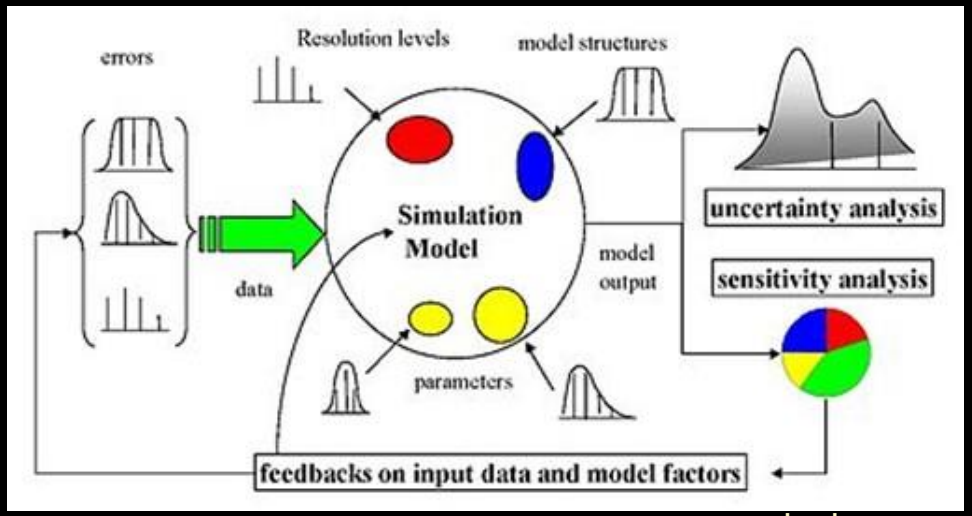
"Sensitivity Analysis is the study of how variation in the output of a model can be apportioned, qualitatively or quantitatively, to different sources of variation (input) and how the given model depends upon the information fed into it."

- Saltelli

Intent is to elucidate the sensitivity of the real-world system to potential changes in the variables and parameters of the system

Sensitivity Analysis Methodology



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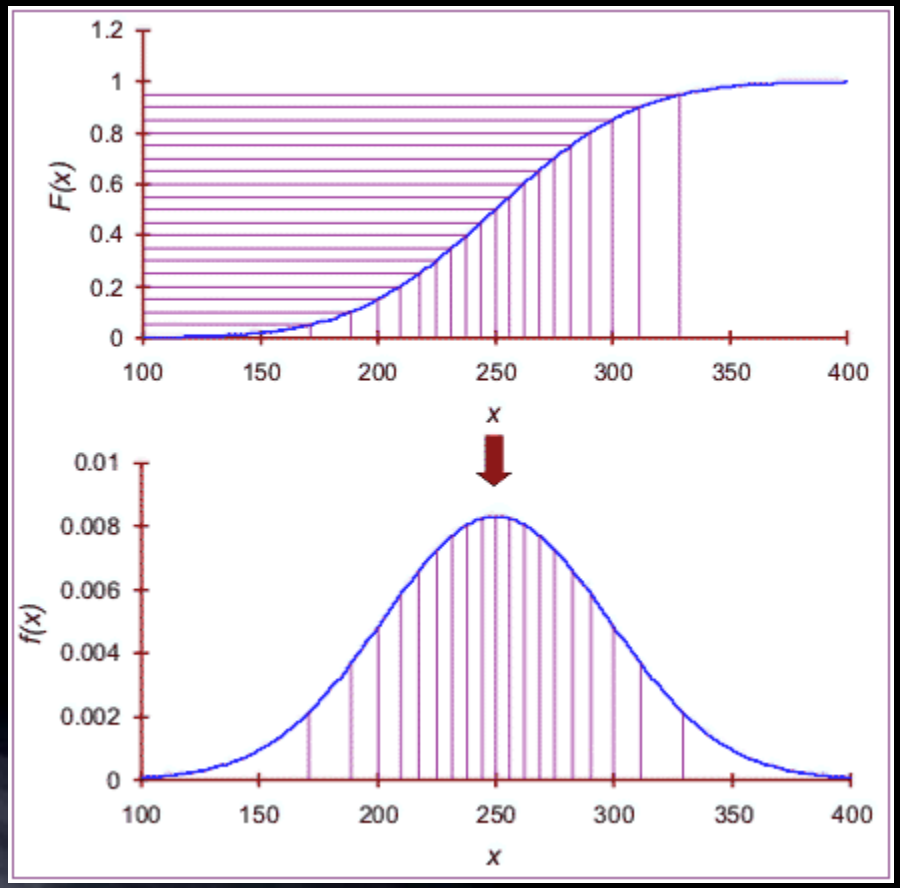
- Partial Rank Correlation Coefficient (PRCC) Analysis
  - Provides a measure of the linear relationships between input parameters and output parameters when all linear effects of other variables are removed after rank transformation.
  - Rank Transformation: non-linear monotonic relations to linear.
  - Used In Models of
    - Cell signaling pathways, infections disease progression, gene expression

Efficient Interrogation of Parameter Space
Latin Hypercube Sampling

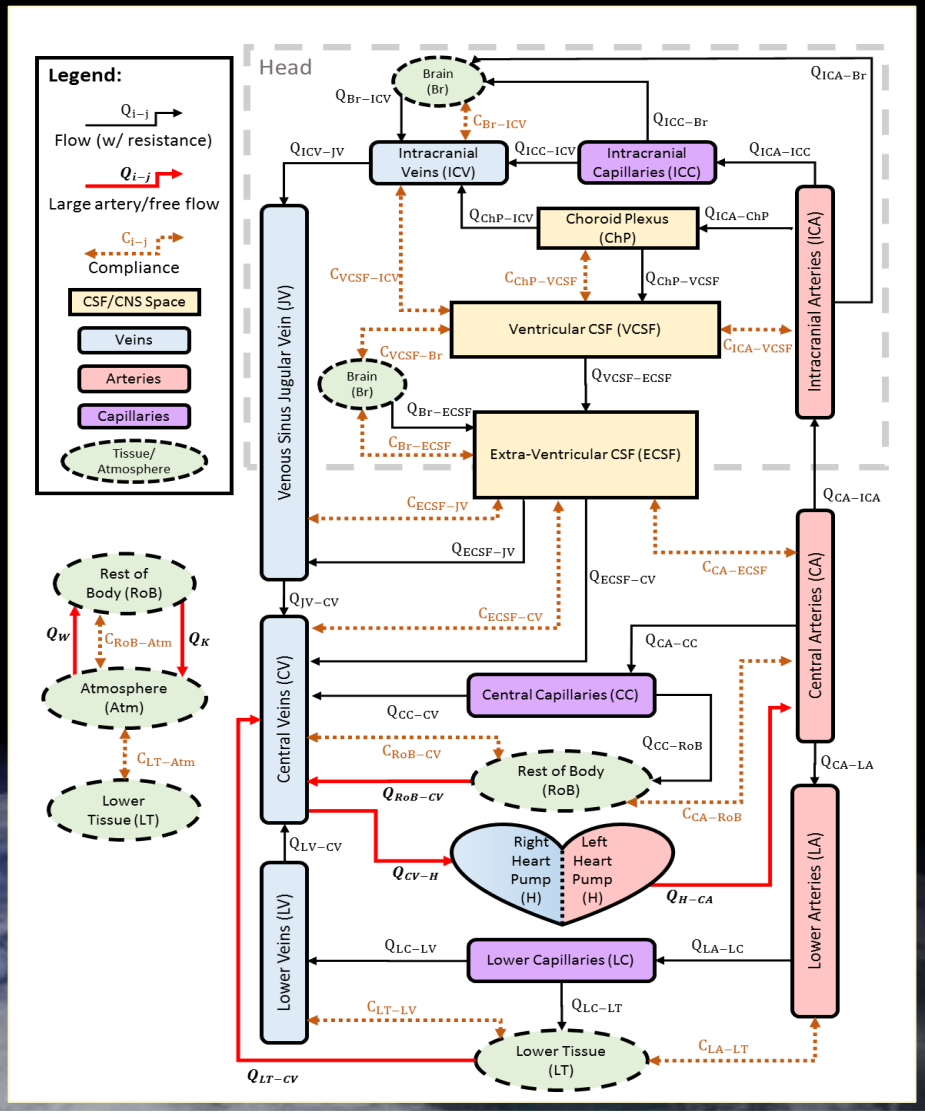
Latin Hypercube Sampling (LHS)

- Sampling method without replacement
- Improved sampling of distribution “tails”
- Can achieve statistical convergence in fewer samples than standard Monte Carlo sampling by as much as 30%
- Is not affected by the number or size of the parameter space in achieving convergence efficiency



https://mathieu.fenniak.net/latin-hypercube-sampling/0

Lumped Cardiovascular System Model: Modified Lakin et al: 16-compartment model



- Lumped Spatial (0-D) unsteady model
  - 16 Compartments
    - 11 blood, 3 CSF, 1 brain, 2 interstitial lymphatic

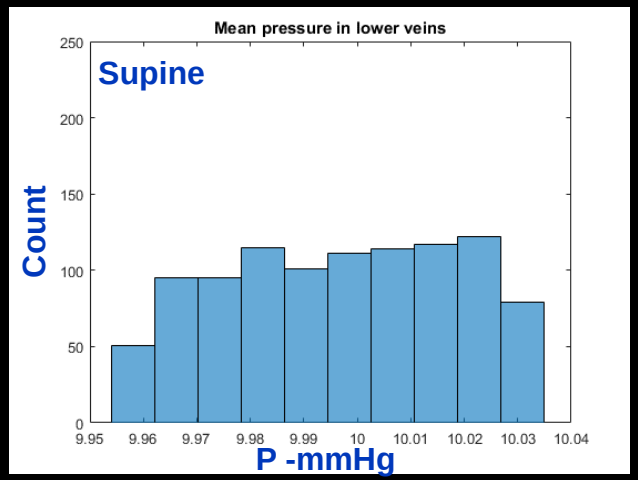
$$[c] * \left[\frac{dp}{dt}\right] + [z] * [P] = [Q]$$

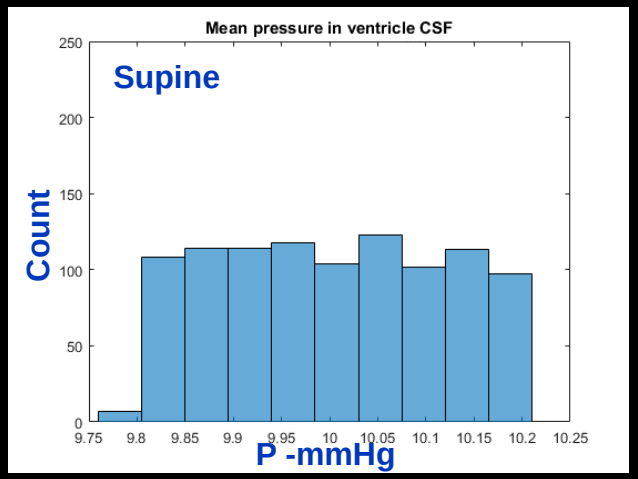
- Compartments represented at 3 heights
  - cranial, upper, lower
- Baroreflex regulation of arterial pressure included

CVS Parameter Analysis

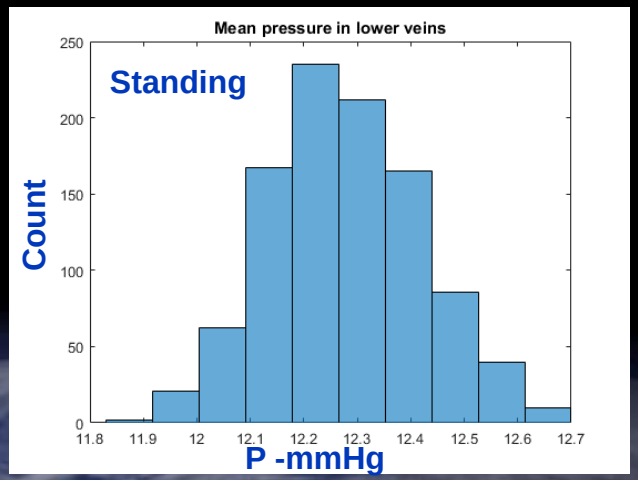
- 42 physiological parameters describe compartments
  - Supine steady-state parameters
  - For sensitivity analysis, each compartment utilizes mean supine pressures and flow rates with the physiological parameters to assess a:
    - Fixed distensibility or compliance per compliance interface
    - Fixed inter-compartment resistance per flow interface
- Estimates of Parameter ranges
  - Range set at +/-10% (uniform distribution)
  - Model trained at cardiac output of 5000 ml/min
  - Simulations performed are at 6900 ml/min in supine and standing configurations for ~2.5 Minutes of simulation time
- Note: Pressures in mmHg, flows in ml/min

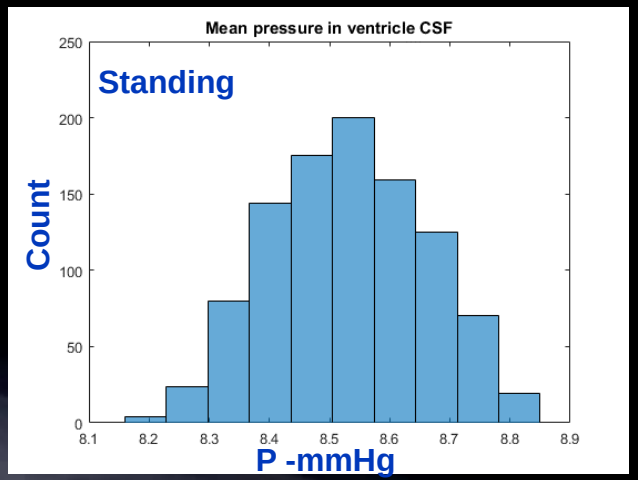
Histograms of Select Pressures





Supine: Small variations in pressure, uniformly distributed

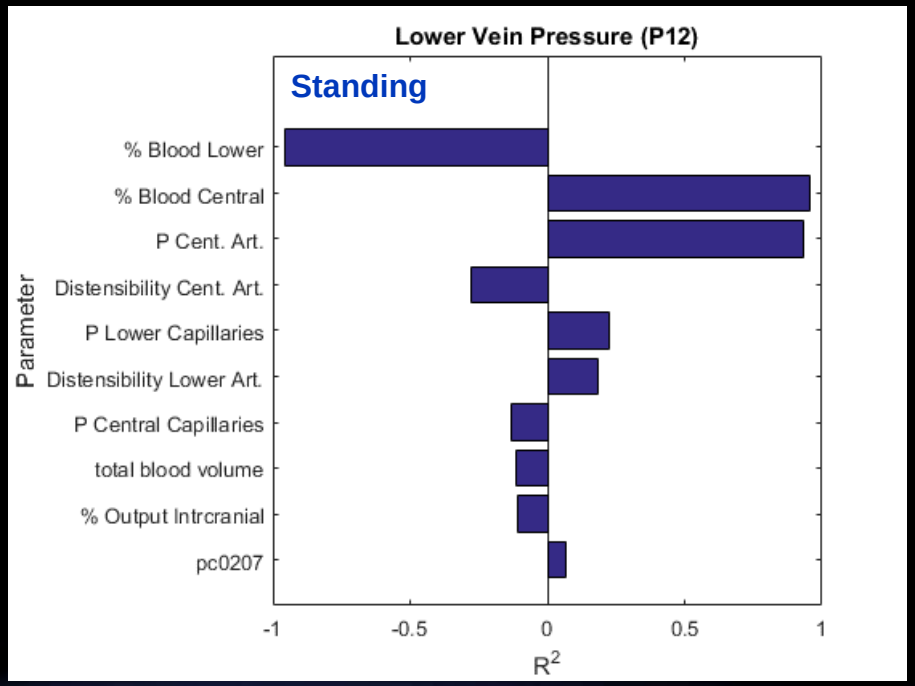


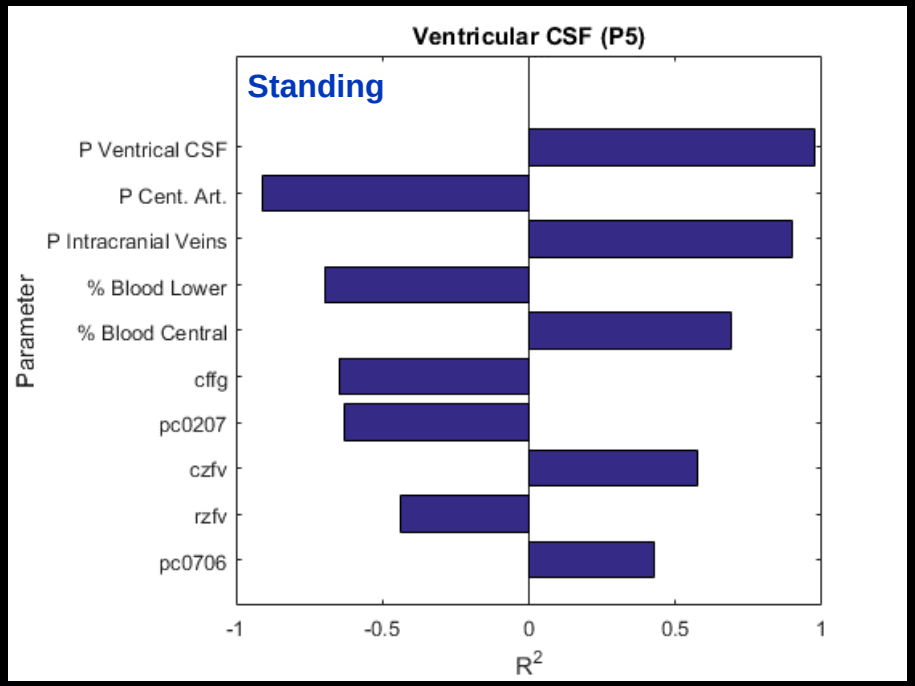


Standing: Larger variations in pressure, near normally distributed

- Represents 1000+ trials, with 100 discretizations of each LHS distribution
- Convergence is estimated as < 0.002 change in output standard distribution per 100 trials

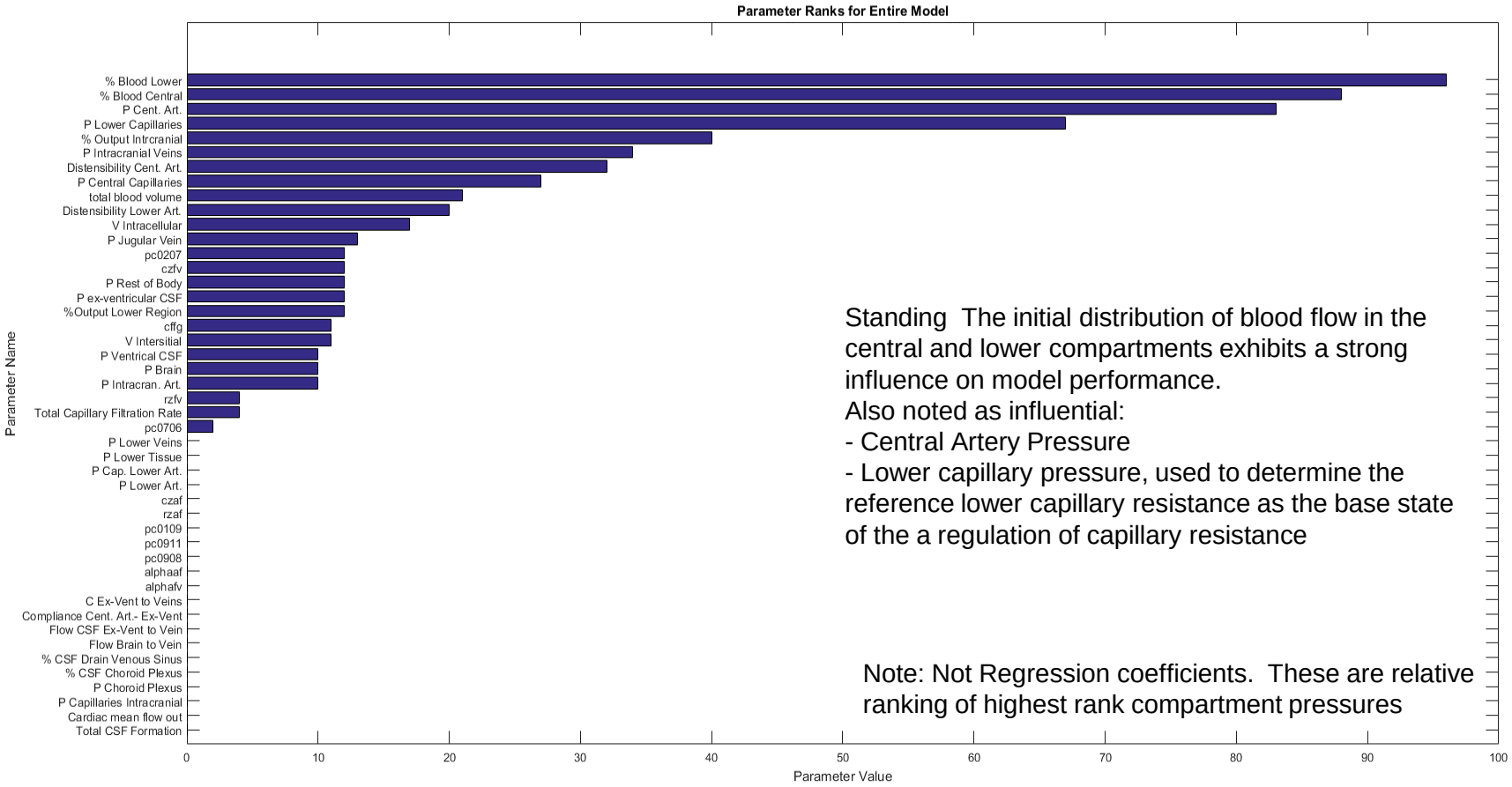
PRCC Sensitivity Analysis Results For Output Pressures





- Supine position sensitive to initial Central Arterial Pressure
  - Venous pressure dominated by variations in initial flow
  - CSF space by initial compartment pressure.
- Standing position sees the same types of trends

Estimated Total Sensitivity of Model



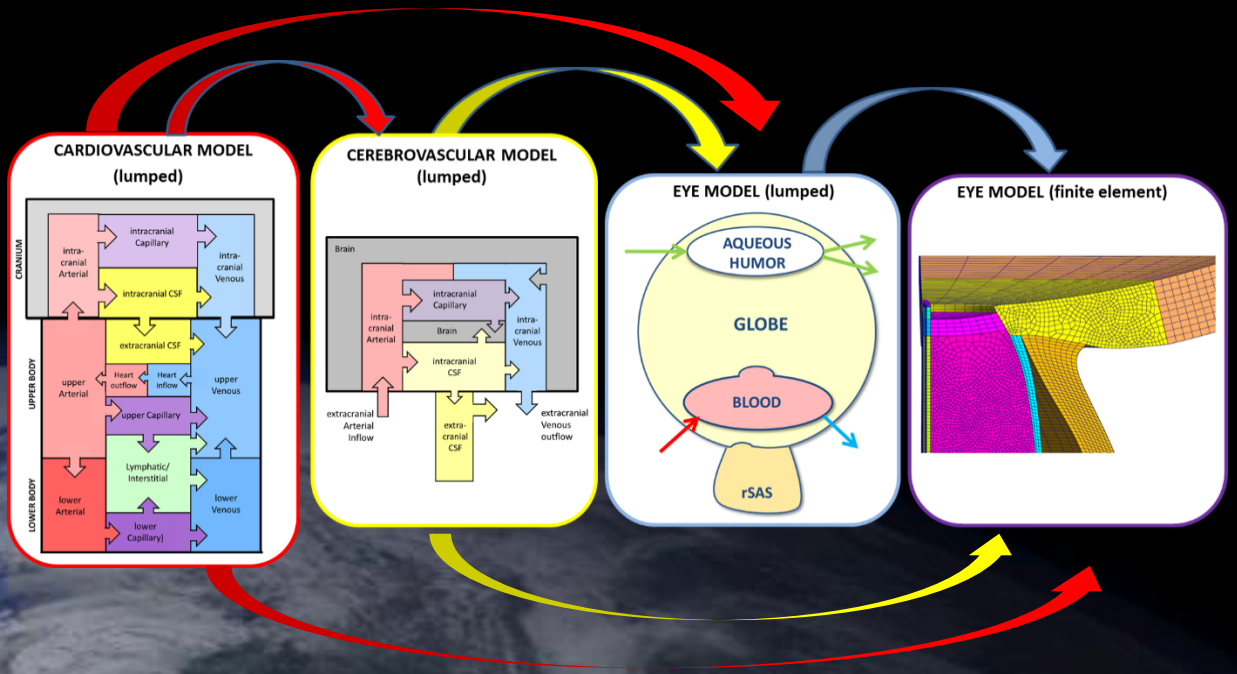
Standing The initial distribution of blood flow in the central and lower compartments exhibits a strong influence on model performance.
Also noted as influential:
- Central Artery Pressure
- Lower capillary pressure, used to determine the reference lower capillary resistance as the base state of the a regulation of capillary resistance

Note: Not Regression coefficients. These are relative ranking of highest rank compartment pressures

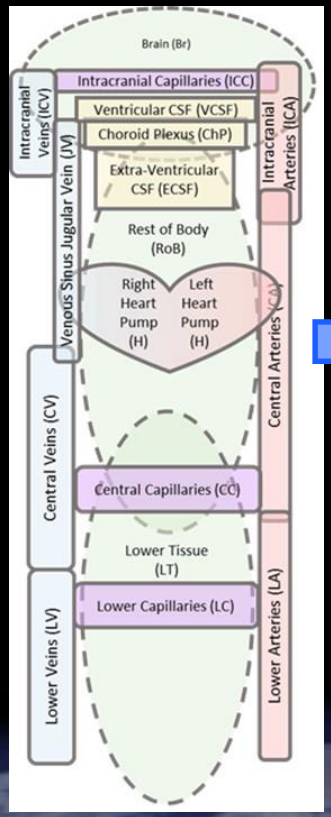
VIIP Modeling: Structured Approach

The suite of lumped parameter models should have the following capabilities:

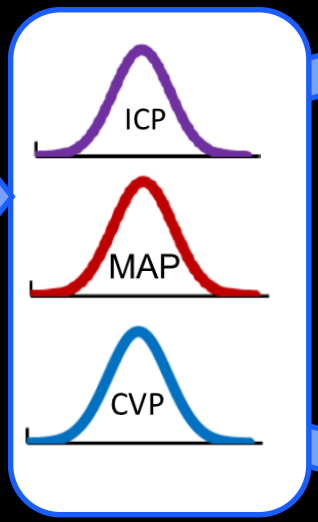
- Bridge the gap between whole-body fluid shift in μg and biomechanical response of ocular tissues
- Identify parameters that have the most effect on *IOP* and *ICP* in μg
- Provide a platform to explore the physiological envelope and find patterns of behavior

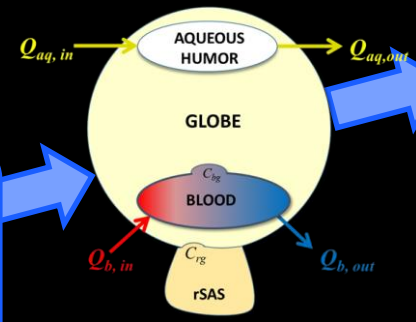


How can this be used in the integrated model of VIIP?

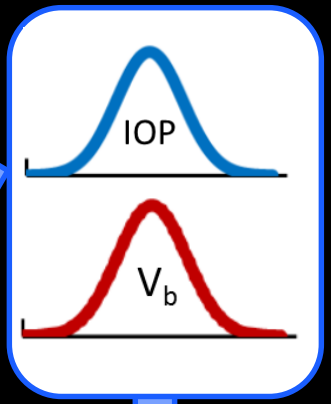


WHOLE BODY

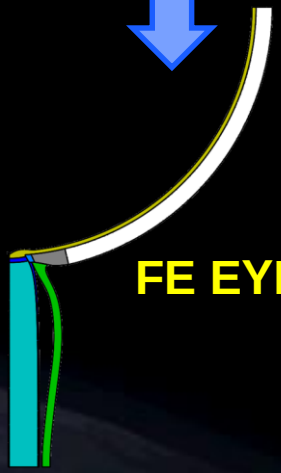




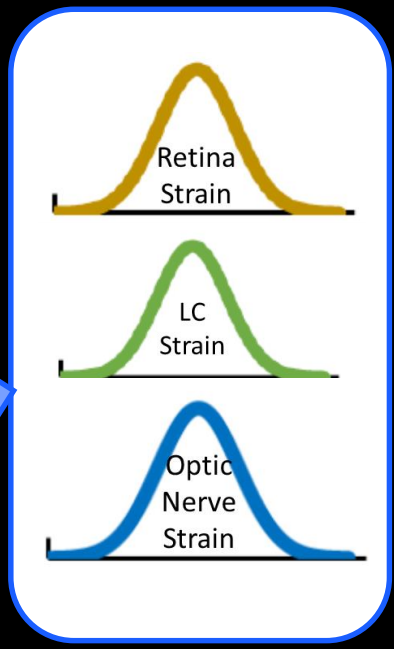
LP EYE



Material Properties



FE EYE

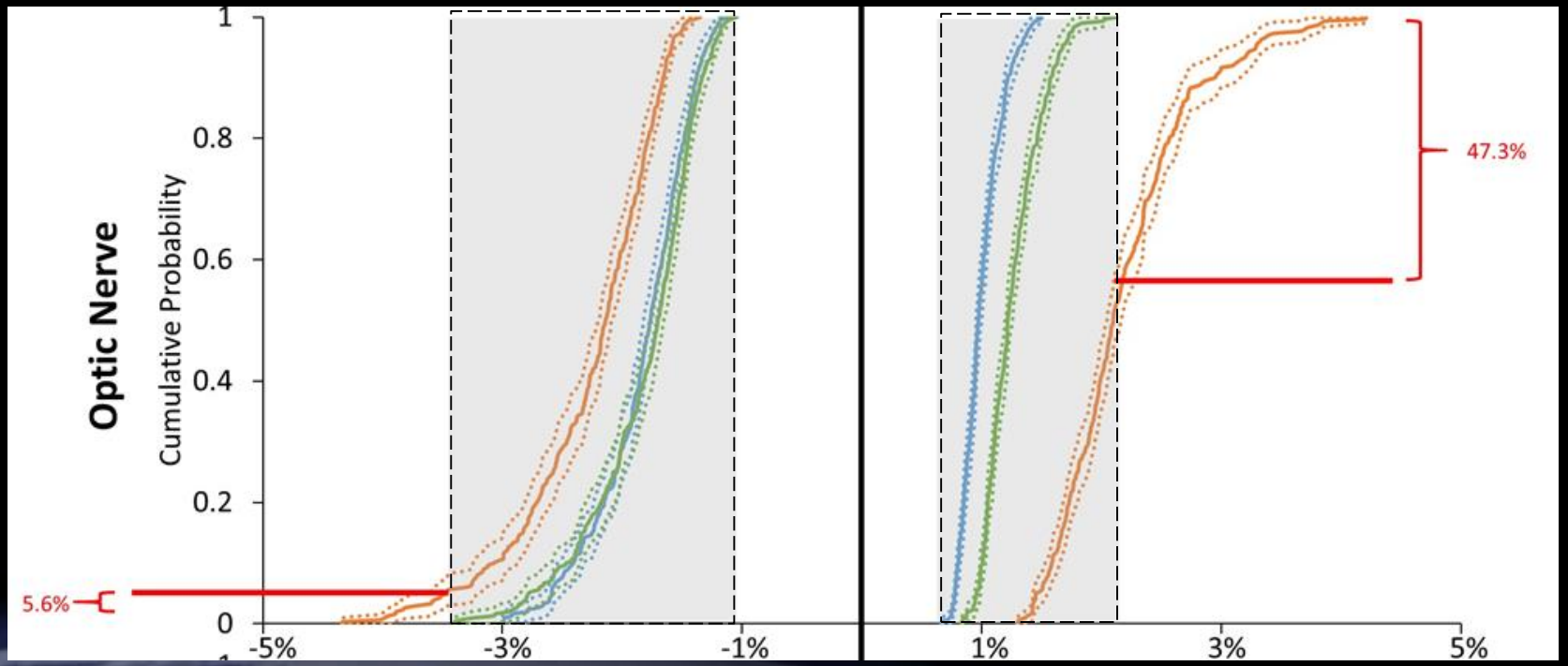


Platform provides a set of ***consistent*** data for exploring the physiological envelope and for finding patterns of behavior in altered g scenarios

Peak Strains in the Optic Nerve

Peak Compression

Peak Tension



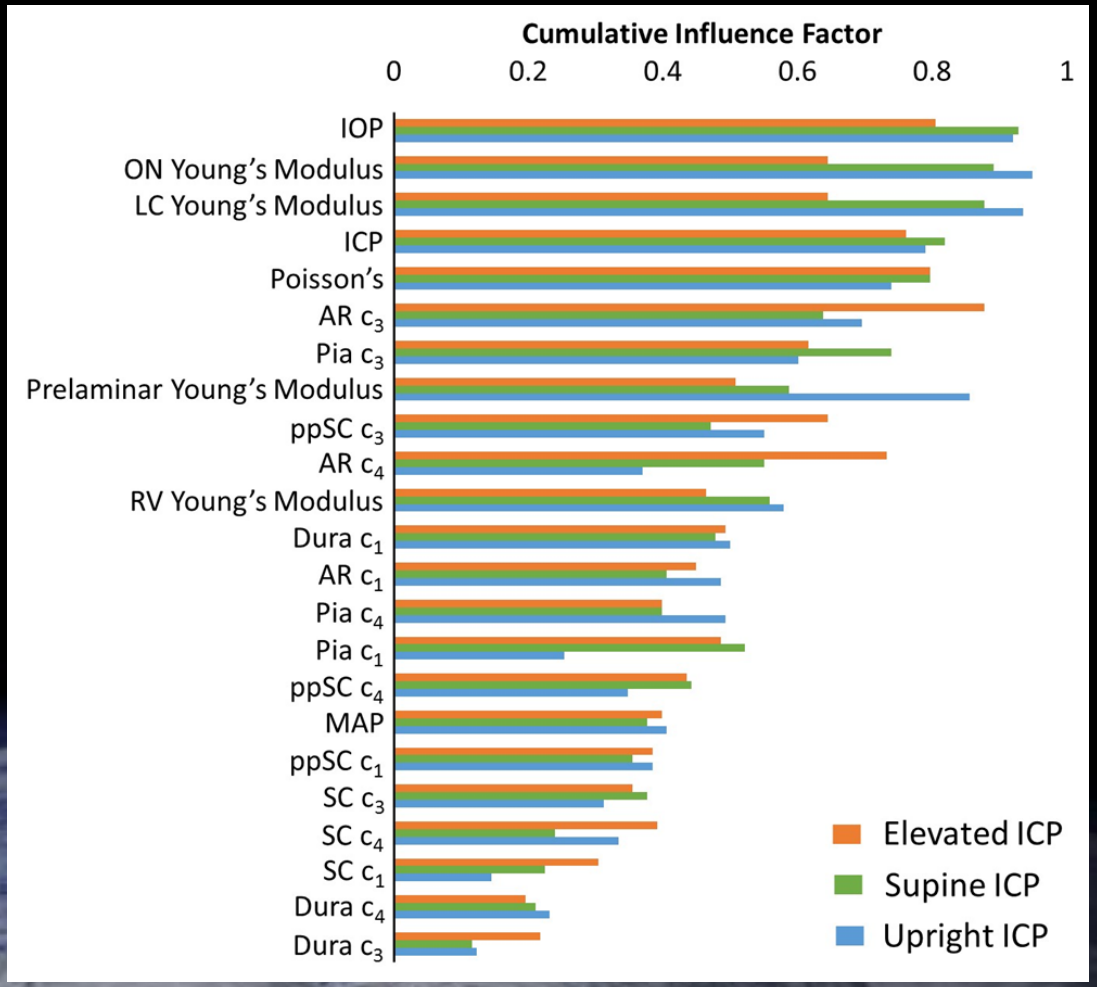
Red indicates % of simulations that fell outside the normal physiological strain range

Peak Strain (%)

Feola et al. Invest Ophthalmol Vis Sci. 2016

Dotted gray box indicates the normal physiological strain range under 1g conditions

Cumulative Influence Factor



Cumulative influence factor for all model inputs shows that:

- IOP and ICP are particularly influential
- ON and LC stiffnesses have large effect on ONH
- C1 – C4 represent the Mooney-Rivlin solid embedded with collagen fibers

Conclusions

- Sensitivity analysis of lumped CVS model identified parameters of strongest influence and population performance
  - As expected, most sensitive parameters change with model orientation
    - Central Artery Pressure, a corollary to MAP, is influential in both orientations
  - Arterial flow distribution appears to be the major influence in standing
    - Regulatory mechanisms likely damp some effects, although they exhibit sensitivities to calculated reference values of regulated parameters
- Extending uncertainty propagation techniques results in powerful method for examining the population parameter space
  - FEM- ONH study found that that c. 47% of individuals would experience “extreme strains” in the optic nerve under assumed microgravity conditions
    - These strains may be sufficient to induce connective tissue remodeling
    - Note: This simulated population with extreme strains is comparable to the (presumably) 41% of astronauts suffering from VIIP syndrome
  - These CDFs also identified ICP, IOP, ON, and LC stiffness as influencing these extreme strains

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Dr. DeVon Griffin – Digital Astronaut Project Manager

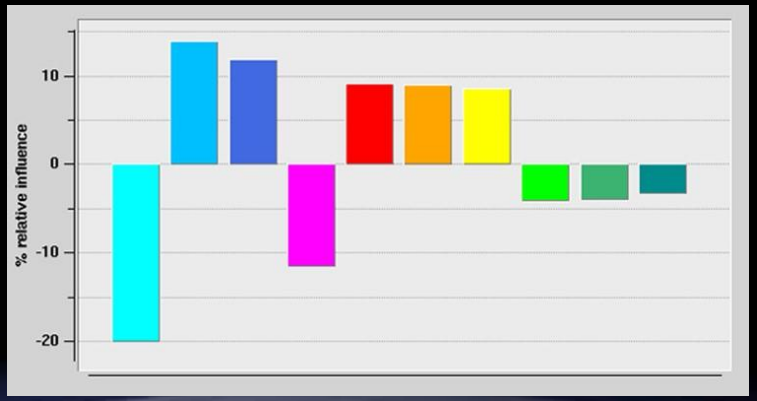
Kelly Gilkey – Digital Astronaut Deputy Project Manager

Questions?

Results Robustness : Sensitivity Analysis

The characteristic that the result from an M&S does not change in a meaningful way to relatively slight variations in parameters.

- Robust if output is relatively stable with respect to changes in input parameters
- Sensitive parameters produce large changes in results from small perturbations



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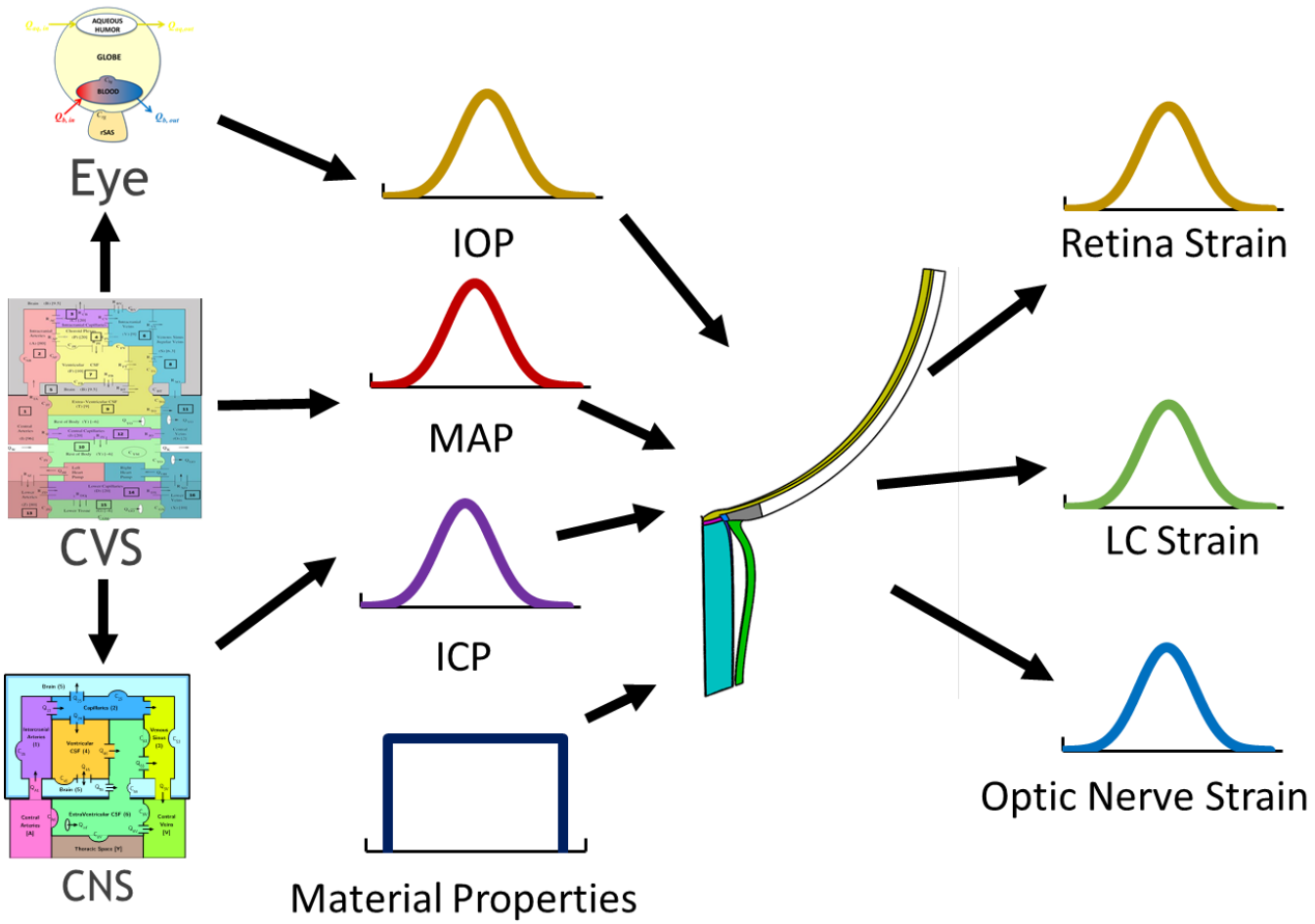
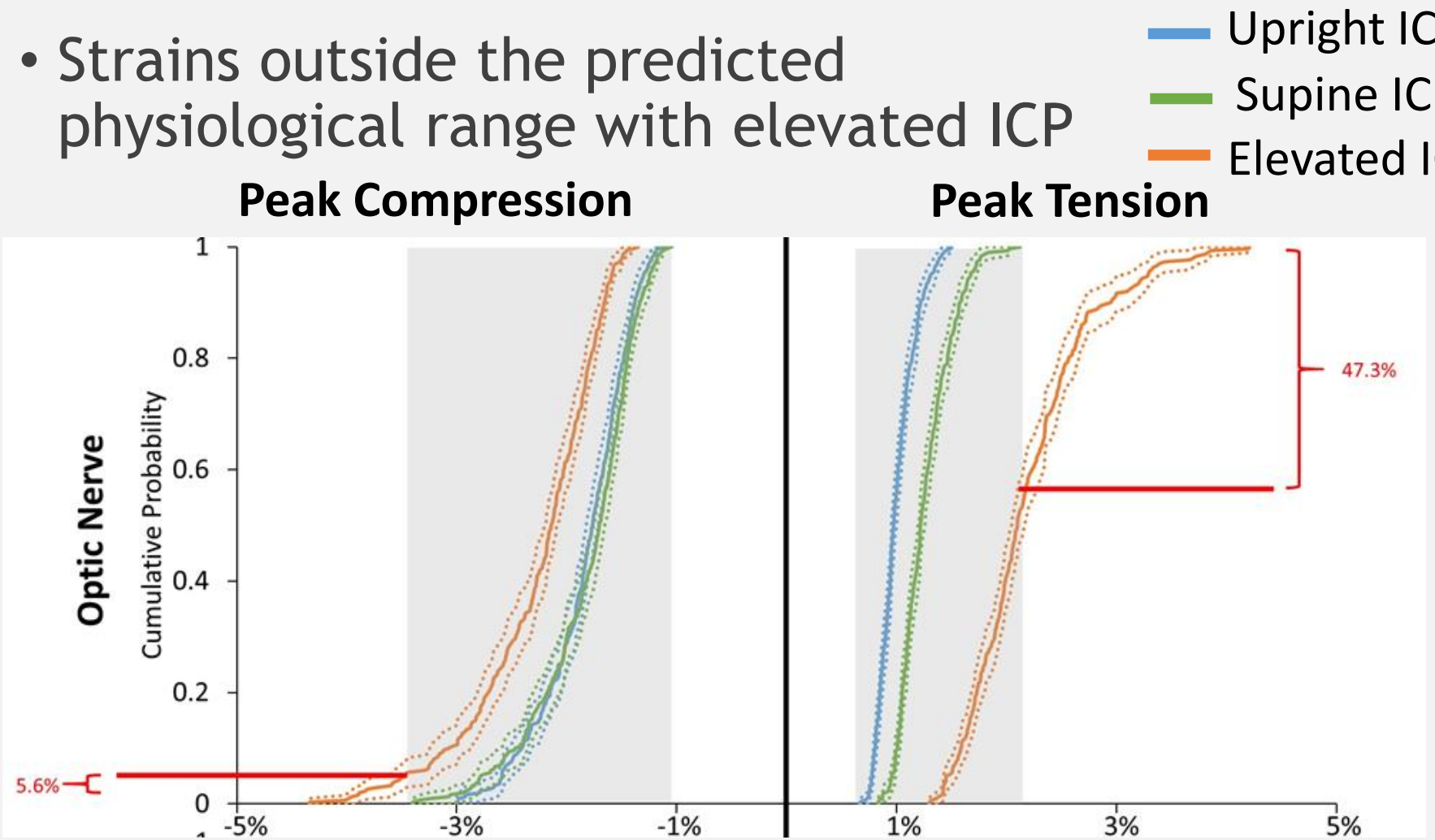


Optic Nerve

- Strains outside the predicted physiological range with elevated ICP



Feola et al. Invest Ophthalmol Vis Sci. 2016

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